REMARKS

Claims 1, 2, 4-15, 20-24, 26-31 were pending. Claims 1 and 21 have been amended herein. New claims 32-40 have been added, support for which can be found throughout the application and, for example, in Table 1. Upon entry of the present amendment, claims 1, 2, 4-15, 20-24, and 26-40 will be pending. No new matter has been added.

I. The Claimed Invention Is Novel and Not Obvious

A. *The Fire Reference*

Claims 21-23 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Fire *et al.*, Nature, 1998, 391, 806-811 (hereinafter the "Fire reference"). Applicants have amended claim 21 to recite a method of interfering with a function of RNA in a cell comprising contacting a cell with an antisense compound "of claim 1" capable of modulating an endogenous RNA-mediated interference pathway. The Fire reference does not discuss or even suggest compounds of claim 1 and therefore cannot anticipate the present invention.

In view of the foregoing, Applicants respectfully request that rejection under 35 U.S.C. §102(b) be withdrawn.

B. The Koesters Reference

Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. §102(b) and §103(a) as allegedly anticipated and/or obvious by Koesters *et al.*, *Genomics*, **1999**, *61*, 210-218 (hereinafter the "Koesters reference"). According to the Office, the Koesters reference reports compounds that would specifically hybridize and inhibit the expression of EIF2C1 because the compounds are 100% identical to the target sequence and, without countervailing evidence, it is assumed that the compounds would inhibit the expression of EIF2C1.

Although Applicants respectfully disagree, solely to advance prosecution, Applicants have amended claim 1 to recite that the compounds inhibit the expression of EIF2C1 by "at least 42%." As the Office is well aware, for a reference to be anticipating it must teach every limitation recited in the claims. There is nothing in the Koesters reference that teaches that the compounds would inhibit the expression of EIF2C1 by at least 42%. As pointed out by the Office, referring to MPEP 2112.01, "the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product." Applicants draw

the Examiner's attention to Table 1 of Applicants' specification (see, pages 83-84) where some of the recited compounds show less than 42% inhibition. Thus, simply because an oligonucleotide may serve as a primer for PCR or sequencing does not necessarily mean that the same oligonucleotide will also have a recited level of bioactivity.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b)/§102(e) and/or §103(a) be withdrawn.

C. The Schalling Reference

Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. §102(e) and §103(a) as allegedly anticipated and/or obvious by U.S. Patent No. 5,695,933 (hereinafter, the "Schalling reference"). According to the Office, the Schalling reference reports compounds that would specifically hybridize and inhibit the expression of EIF2C1 because the compounds are 100% identical to the target sequence and, without countervailing evidence, it is assumed that the compounds would inhibit the expression of EIF2C1.

Although Applicants respectfully disagree, solely to advance prosecution, Applicants have amended claim 1 to recite that the compounds inhibit the expression of EIF2C1 by "at least 42%." As the Office is well aware, for a reference to be anticipating it must teach every limitation recited in the claims. There is nothing in the Schalling reference that teaches that the compounds would inhibit the expression of EIF2C1 by at least 42%. As pointed out by the Office, referring to MPEP 2112.01, "the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product." Again, Applicants draw the Examiner's attention to Table 1 of Applicants' specification (see, pages 83-84) where some of the recited compounds show less than 42% inhibition. Thus, simply because an oligonucleotide may serve as a primer for PCR or sequencing does not necessarily mean that the same oligonucleotide will also have a recited level of bioactivity.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) and/or §103(a) be withdrawn.

II. The Claimed Invention is Not Obvious

D. The Combination of the Koesters, Cikaluk, Taylor, Baracchini, and Milner References

Claims 1, 2, 4-15, 20, 24, and 28-31 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Koesters reference in view of Cikaluk *et al., Mol. Biol. Cell*, **1999**, *10*, 3357-3372 (hereinafter the "Cikaluk reference"), Taylor *et al., Drug Discovery Today*, **1999**, *4*, 562-567 (hereinafter the "Taylor reference"), U.S. Patent No. 5,801,154 (hereinafter the "Baracchini reference"), and Milner *et al., Nature Biotechnology*, **1997**, *15*, 537-540 (hereinafter the "Milner reference"). Applicants traverse the rejection and respectfully request reconsideration of the same because the Office has failed to establish a *prima facie* case of obviousness. In addition, the Office has failed to provide any motivation to modify the cited references so as to render the present claims obvious.

The Office alleges that it would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to design and use antisense molecules for the specific inhibition of EIF2C1 expression because the sequence for EIF2C1 was previously taught and because the Taylor reference reports that antisense oligonucleotides can be designed to inhibit any gene of known sequence. The Office also alleges that one of ordinary skill in the art would have been motivated to inhibit EIF2C1 because the Koesters reference reports elevated expression of EIF2C1 in tumors and because the Taylor reference reports that antisense inhibition is valuable as a research tool to elucidate gene function. The Office also alleges that the Cikaluk reference provides motivation because it reports inhibiting the ortholog in *C. elegans* using RNA interference (Office Action, page 12).

The Cikaluk reference reports GERp95, a membrane-associated protein that belongs to a family of proteins involved in stem cell differentiation. The Cikaluk reference, however, fails to teach or even suggest a nucleotide sequence that is identical to SEQ ID NO:3 of the present application. The Cikaluk reference also fails to teach or even suggest compounds that are 8 to 50 nucleobases in length that inhibit the expression of EIF2C1 by at least 42%, and/or wherein the compounds comprise at least one modified internucleoside linkage. Furthermore, the Cikaluk reference fails to teach or even suggest methods of interfering with the function of a nucleic acid in a cell using a compound that is 8 to 50 nucleobases in length that specifically hybridizes with a nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1 by at least 42%.

Indeed, the Cikaluk reference is silent as to the size the RNA that is used in its experiments to elucidate the function of GERp95 in *C. elegans*.

The Koesters reference reports EIF2C1 but fails to teach or even suggest a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1 by at least 42%. Furthermore, the Koesters reference fails to teach or even suggest the elements recited in claims that are dependent on claim 1. For example, the Koesters reference fails to teach embodiments of claim 1 wherein the compounds are antisense oligonucleotides, wherein the compounds comprise at least one modified internucleoside linkage, at least one modified sugar moiety, at least one modified nucleobase, and/or the antisense oligonucleotide is a chimeric oligonucleotide. The Koesters reference also fails to teach compounds 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding EIF2C1. The Koesters reference also fails to teach a composition comprising the compound of claim 1 and pharmaceutically acceptable carrier or a method of inhibiting the expression of EIF2C1 in cells or tissues comprising contacting the cells or tissues with the compound of claim 1 so that the expression of EIF2C1 is inhibited. The Koesters reference further fails to teach the subject matter of claims 28 and 29, *i.e.*, embodiments wherein the modulation of EIF2C1 expression is at least 60% or 80%.

The Taylor reference fails to compensate for the deficiencies of the Koesters reference. The Taylor reference reports antisense oligonucleotides and a systematic high-throughput approach to target validation and gene function determination but fails to teach or even suggest a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1 by at least 42%. Indeed, the Taylor reference fails to even discuss the EIF2C1 gene, much less compounds that target and inhibit EIF2C1 expression. Furthermore, the Taylor reference fails to teach or suggest the elements recited in claims that are dependent on claim 1, as discussed above.

The Baracchini reference reports antisense oligonucleotide modulation of multidrug resistance-associated protein but fails to compensate for the deficiencies of the Koesters reference and the Taylor reference. The multidrug resistance-associated protein is not equivalent or even

related to EIF2C1. The Baracchini reference fails to teach or even suggest a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1 by at least 42%. The Baracchini reference fails to ven discuss the EIF2C1 gene, much less compounds that target and inhibit EIF2C1 expression. Furthermore, the Baracchini reference fails to teach or suggest the elements recited in claims that are dependent on claim 1, as discussed above.

The Milner reference reports the selection of effective antisense reagents on combinatorial oligonucleotide arrays but fails to compensate for the deficiencies of the Koesters reference, the Taylor reference , the Cikaluk reference, and the Baracchini reference. The Milner reference fails to teach a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1 by at least 42%. Indeed, the Milner reference fails to even discuss the EIF2C1 gene, much less compounds that target and inhibit EIF2C1 expression. Furthermore, the Milner reference fails to teach or suggest the elements recited in claims that are dependent on claim 1, as discussed above.

As is clear from MPEP 2143, in order to provide a *prima facie* case of obviousness, the Examiner must first establish motivation to combine or modify the references.

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

(MPEP 2143). The Office has not only failed to provide motivation, but also failed to provide a reasonable expectation of success.

None of the references cited in the Office Action suggest using compounds 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1 by at least 42%. None of the r ferences cited by the Office suggest modifying any reference or any composition as to yield the claimed invention.

Additionally, none of the references cited by the Office suggest making and/or using such a compound that specifically hybridizes with a nucleic acid molecule encoding EIF2C1 comprising at least one modified internucleoside linkage, an antisense oligonucleotide, a modified internucleoside linkage that is a phosphorothioate linkage, at least one modified sugar moiety, a 2'-O-methoxyethyl sugar moiety, at least one modified nucleobase, 5-methlycytosine, or a chimeric oligonucleotide and that inhibits the expression of EIF2C1. Of the four references cited by the Office, only one even identifies the EIF2C1 gene.

There is no motivation within the references, nor has one been identified by the Office, to combine the references in the manner suggested in the Office Action in such a way as to yield the claimed invention. The references do not refer to one another either explicitly or implicitly. It appears that the only motivation that the Office is using to combine the references is the use of the Applicants' specification and hindsight reconstruction, which is strictly forbidden. Accordingly, the combination of references is improper for its use of hindsight reconstruction based upon Applicants' disclosure.

The general motivations provided by each of the Taylor, Baracchini, and Milner references does not comport with the level of obviousness required under the law. In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

Significantly, the Office identifies no "motivating force" attributed to the Taylor, Baracchini, and Milner references that would "**impel**" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention, let alone combine the teachings of the cited references in the manner suggested by the Office. The alleged motivation is, at best, an invitation for further experimentation and, at most, provides an "obvious to try" situation.

However, "obvious to try" is not the standard of 35 U.S.C. §103. *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987).

The combination of the references also does not provide one of skill in the art an "expectation of success." There is ***nothing*** within the references, either alone or in combination, that would lead one of skill in the art to expect that antisense molecules would inhibit the expression of EIF2C1 by at least 42%. As can be seen in Table 1, some compounds did not inhibit the expression of EIF2C1 by at least 42%. Before the present invention, it could not be known and was not known or expected that antisense molecules would be able to inhibit the expression of EIF2C1 by at least 42%. Without this expectation, the present claims ***cannot*** be obvious in view of the cited references. Until the present invention there was no evidence that inhibition of EIF2C1 by at least 42% could occur. Therefore, the claimed invention is ***not*** obvious. If in a subsequent Office Action, the Office still deems that the pending claims are obvious even in view of Applicants' amendment, Applicants respectfully point out that using Applicants' specification as a blueprint for a rejection is strictly prohibited. There is ***no*** teaching or suggestion within the combined references to inhibit the expression of EIF2C1 by at least 42%.

The references also do not teach or suggest the compounds of the present invention wherein the compounds specifically hybridize to the 5' untranslated region, the start codon region, the coding region, the stop coding region, or the 3' untranslated region of the nucleic acid molecule encoding EIF2C1 or the specific SEQ ID NOs. The references alone or in combination do not provide motivation or an expectation of success for one of skill in the art to make the specific oligonucleotides that inhibit the expression of EIF2C1 by at least 42%.

Thus, in view of the foregoing, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

III. The Claimed Invention Is Enabled

Claims 15, 20-24, 26-28 and 30 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to provide an enabling disclosure. The Office asserts that although the specification is enabling for a method of inhibiting the expression of EIF2C1 in cells *in vitro*, the specification does not reasonably provide enablement for *in vivo* antisense-mediated modulation

of an endogenous RNA-mediated interference pathway and for inhibiting the expression of EIF2C1 *in vivo*. Applicants traverse the rejection and respectfully request reconsideration of the same.

The Office maintains the rejection using the same arguments from the previous rejection and additionally cites a new reference (Agami, *Curr. Opin. Chem. Bio.*, **2002**, *6*, 829-8334, hereinafter the "Agami reference") to support its allegation that antisense compounds and antisense technology is unpredictable *in vivo*. According to the Office, the Agami reference reports that since RNAi compounds are nucleic acid oligonucleotides applications involving RNAi. Thus, according to the Office, they are "subject to the same unpredictabilities as outlined in previous Office actions." (Office Action, page 3). Applicants respectfully disagree that the Agami reference would lead one of skill in the art to believe that RNAi technology or antisense technology is unpredictable.

The Agami reference states:

> Using this [RNAi] method it was possible to suppress gene expression to the extent that the gene function is lost and to inhibit the replication of HIV and RNA viruses in human cells. As it stands, the application of siRNAs for disease and gene therapies can follow the existing tools that are already applicable for clinical trials of anti-sense strategies to inhibit gene expression. However, a major drawback of this technology is its transient effect. Gene could only be inactivated for a week.

(Agami, p. 832, right column). Nothing in the Agami reference states that RNAi will not work *in vivo*. The only limitation that the Agami reference discusses is getting persistent inhibition (*i.e.* more than one week). The length of time that the expression of EIF2C1 is inhibited or that the function of a nucleic acid is interfered with, however, is ***not*** a feature of the claims. The transientness of a particular compound may ultimately be important for a compound to be approved as a drug by the FDA, but this is not relevant to the patentability of the present claims.

It appears that, as in the previous Office Actions, the Office is repeating the same mistake it has made before and confusing efficacy of a compound (*i.e.* whether the compound can ultimately cure a disease) with whether the claims are patentable. Further support of Applicants' arguments that the Office is improperly importing limitations into the claims can be found throughout the Office Action. For example, the Office cites Crooke *et al.*, which according to the office, states "extrapolations from *in vitro* uptake studies to predictions about *in vivo*

pharmacokinetic behavior are entirely inappropriate...one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies." (Office Action, page 3). Whether or not the statement by Crooke is true ***does not*** matter. Applicants are not claiming a method of predicting "*in vivo* pharmacokinetic behavior." Rather Applicants are claiming methods of inhibiting expression of EIF2C1, a method of modulating the process of RNA-mediated interference (RNAi), a method of inhibiting translation initiation in a cell, a method of interfering with a function of RNA in a cell, and a method of inhibiting translation initiation complex formation in a cell using the compounds of the present invention. One of skill in the art does not need to know the pharmacokinetic behavior to practice the present invention. "*In vivo* pharmacokinetic behavior" may be and is likely important for the efficacy of a drug that is to be approved by the FDA, but it s not relevant to the pending claims. Even if the compounds of the present invention inhibit the expression of EIF2C1 for a fleeting amount of time, the method is still embraced by the claims and is enabled.

The Office also re-cites Gewirtz, which according to the Office, states, "Without [the] ability [to deliver ODN into cells and have them reach their target], it is clear that even an appropriately targeted sequence is not likely to be efficient." (Office Action, page 4). Whether the compounds of the present invention are "efficient" is not of a concern for the Office in considering the patentability of the pending claims. "Efficiency" is not a feature of the claims and should not be considered when reviewing the claims. Applicants respectfully remind the Office that importing limitations into the claims is strictly forbidden.

In Applicants' previous response, several research articles were submitted as proof that one of skill in the art would expect that if compounds inhibit the expression of a compound *in vitro* there would be an expectation and a correlation that the compounds would have similar activity *in vivo*. The Office alleges that these references were not persuasive because "the results from these single experiments, performed in organisms not found in nature, do not outweigh the multitude of art in the 5 review articles provided and cited in previous Office Actions." (Office Action, page 6). Applicants respectfully disagree.

As an initial matter, Applicants respectfully disagree that the papers submitted by Applicants use "organisms not found in nature." Although, some of the mice may have been generated to be immuno-compromised, there are numerous organisms in "natur " that are also immuno-compromised (*e.g.* individuals with HIV, cancer, and the like). Wheth r or not these

organisms are found in "nature" is not relevant to the pending claims. Whether or not these experiments would be satisfactory for the compounds to be approved by the FDA is unknown. Further, it is completely irrelevant to the discussion of patentability whether "most injected oligonucleotides stimulate a disproportionately high non-specific immune response in mammals" as alleged by the Office (see, page 5 of the Office Action). Indeed, whether any compound of the present invention induces any immune response is irrelevant to patentability -- i.e, the compounds of the present invention can have any side effect and still be patentable. The experiments in the references submitted by Applicants, however, **clearly show that compounds that work *in vitro* also work *in vivo* and that one of skill in the art would accept that there is a correlation between *in vitro* and *in vivo* results.**

It appears that the crux of the Office's rejection is that one of skill in the art would have to practice undue experimentation to use the compounds of the present invention to be approved by the FDA because all the evidence that Office has cited discusses items like "efficiency," "*in vivo* pharmacokinetics," and the like. As the Federal Circuit has recently reaffirmed, an invention does not have to be ready for commercial use. The court stated:

> Title 35 ***does not*** require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, ***commercially viable embodiment absent a claim limitation to that effect.*** Title 35 requires only that the inventor enable one of skill in the art to make and use the full scope of the claimed invention.

(emphasis added. *CFMT, Inc. and CFM Tehnologies, Inc., v. Yieldup Int'l Corp.* Decided: November 12, 2003). The requirements that the Office desires from Applicants' specification are "absent...to that effect" and therefore, should not be read into the claims. Therefore, whether the claimed methods are "efficient" is not relevant.

Applicants have clearly enabled "one of skill in the art to make and sue the full scope of the claimed invention." In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

IV. Conclusion

Applicants believe the pending claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6914 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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